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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/506,366	02/02/2005	Michele Orlando	14503-010US1	1083

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EXAMINER	
WHITE, EVERETT NMN	
ART UNIT	PAPER NUMBER
1623	

NOTIFICATION DATE	DELIVERY MODE
11/05/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PATDOCTC@fr.com

Office Action Summary	Application No.	Applicant(s)	
	10/506,366	ORLANDO ET AL.	
	Examiner	Art Unit	
	EVERETT WHITE	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 August 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37-78* is/are pending in the application.

4a) Of the above claim(s) *57-73* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37-56 and 74-78* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/11/2009 & 10/14/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 11, 2009 has been entered.

2. The amendment filed August 11, 2009 has been received, entered and carefully considered. The amendment affects the instant application accordingly:

(A) Claims 1-36 were previously canceled;
(B) Claims 37, 38, 40-47, 77 and 78 have been amended;
(C) Comments regarding Office Action have been provided drawn to:
  (I) 102(b) rejection, rendered moot by new ground of rejection over newly cited US Patent.;
  (II) 103(a) rejection, rendered moot by new ground of rejection over newly cited US Patent.

3. Claims 37-78 are pending in the case. Claims 57-73 are withdrawn from consideration as been drawn to non-elected inventions.

Foreign Priority Claimed

4. This application is a 371 of PCT/EP03/02084 International Filing Date: February 28, 2003 published in German, which claims foreign priority to Germany 10209822.0 under 35 U.S.C. 119(a)-(d). It is noted that PCT/EP03/02084 and Germany 10209822.0 (March 6, 2002) are in German, no translation of the documents into English has been provided.

Information Disclosure Statement

5. The information disclosure statement filed August 11, 2009 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all

other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered.

6. The information disclosure statement filed August 11, 2009 fails to comply with 37 CFR 1.98(a)(1), which requires the following: (1) a list of all patents, publications, applications, or other information submitted for consideration by the Office; (2) U.S. patents and U.S. patent application publications listed in a section separately from citations of other documents; (3) the application number of the application in which the information disclosure statement is being submitted on each page of the list; (4) a column that provides a blank space next to each document to be considered, for the examiner's initials; and (5) a heading that clearly indicates that the list is an information disclosure statement. The information disclosure statement has been placed in the application file, but the information referred to therein has not been considered.

Claim Rejections - 35 USC § 112

New Ground of Rejection

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 37-56 and 74-78 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "low" in the phrase "low molecular weight substance" in Claims 37, 39-42, 48, 74 and 76 is a relative term which renders the claim indefinite. The term "low" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Claims depending from Claims 37, 39-42, 48, 74 and 76 are also rejected for the same reason.

8. Applicant's arguments with respect to Claims 37-56 and 74-78 have been considered but are moot in view of the new ground(s) of rejection.

Claim Rejections - 35 USC § 102

New Ground of Rejection

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 37, 40, 41, 45- 47, 48, 50, 74, 77 and 78 are rejected under 35 U.S.C. 102(b) as being anticipated by Sommermeyer et al (US Patent No. 6,083,909, newly cited).

Applicants claim a conjugate of hydroxyalkylstarch (HAS) and a low molecular weight substance, obtained by a process that comprises selectively coupling (i) the terminal aldehyde group of a HAS molecule, or a functional group derived from this aldehyde group by chemical reaction, with (ii) a functional group on the low molecular weight substance, which is able to react with the terminal aldehyde group of the HAS molecule or the functional group derived therefrom, wherein the coupling reaction results in a covalent bond between the terminal aldehyde of the HAS molecule or the functional group derived therefrom and the low molecular weight substance functional group, or wherein the coupling reaction is modified by a further reaction to give the abovementioned covalent bond.

The Sommermeyer et al patent discloses a haemoglobin -hydroxyethylstarch conjugate in which the haemoglobin and the hydroxyethylstarch are linked to one another selectively via amide bonds between free amino groups of the haemoglobin and the reducing end group of the hydroxyethylstarch, which is present in oxidized form (see abstract), which anticipate the instantly claimed conjugate of hydroxyalkylstarch and a low molecular weight substance. Also see column 5, 1st paragraph of the Sommermeyer et al patent, wherein the hydroxyethylstarch thereof is characterized by a molar degree of substitution of 0.1 to 0.8 and a ratio of C_2:C_6 substitution in the range from 2 to 20, which anticipate the subject matter of instant Claims 45 and 46, which

recite a degree of substitution in the range from about 0.3 to about 0.7 and a ratio of C_2 to C_6 substitution of form 8 to 12.

11. Applicant's arguments with respect to Claims 37, 40, 41, 45- 47, 48, 50, 74, 77 and 78 have been considered but are moot in view of the new ground(s) of rejection.

Claim Rejections - 35 USC § 103

New Ground of Rejection

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

13. Claims 37-56 and 74-78 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sommermeyer et al (US Patent No. 6,083,909, newly cited) in view

of Adamson (CA 2233725 A1, already of record) or Harboe et al (EP 331471 A, already of record) or Berger et al (EP 019403 A2, already of record).

Applicants claim a conjugate of hydroxyalkylstarch (HAS) and a low molecular weight substance, obtained by a process that comprises selectively coupling (i) the terminal aldehyde group of a HAS molecule, or a functional group derived from this aldehyde group by chemical reaction, with (ii) a functional group on the low molecular weight substance, which is able to react with the terminal aldehyde group of the HAS molecule or the functional group derived therefrom, wherein the coupling reaction results in a covalent bond between the terminal aldehyde of the HAS molecule or the functional group derived therefrom and the low molecular weight substance functional group, or wherein the coupling reaction is modified by a further reaction to give the abovementioned covalent bond.

The Sommermeyer et al patent discloses a haemoglobin -hydroxyethylstarch conjugate in which the haemoglobin and the hydroxyethylstarch are linked to one another selectively via amide bonds between free amino groups of the haemoglobin and the reducing end group of the hydroxyethylstarch, which is present in oxidized form (see abstract), which embrace the instantly claimed conjugate of hydroxyalkylstarch and a low molecular weight substance. Also see column 5, 1st paragraph of the Sommermeyer et al patent, wherein the hydroxyethylstarch thereof is characterized by a molar degree of substitution of 0.1 to 0.8 and a ratio of C_2:C_6 substitution in the range from 2 to 20, which embrace the subject matter of instant Claims 45 and 46, which recite a degree of substitution in the range from about 0.3 to about 0.7 and a ratio of C_2 to C_6 substitution of form 8 to 12 for the hydroxyalkylstarch.

The instantly claimed conjugate differs from the conjugate of the Sommermeyer et al patent by claiming a linker molecule that links the HAS molecule to the low molecular weight substance, by claiming specific low molecular weight substances not disclosed in the Sommermeyer et al patent, and by claiming a HAS molecule that has a molecular weight not disclosed in the Sommermeyer et al patent.

The Adamson CA publication discloses hemoglobin conjugates prepared by reacting hemoglobin with oxidized hydroxyethyl starch, and allowing the resultant

conjugate to degrade to a lower molecular weight product, after conjugation. Adamson discloses that the conjugate is then reductively stabilized to form secondary amino bonds between the hemoglobin and the hydroxyethyl starch (see abstract). See lines 1-5 on page 4 of the Adamson publication wherein hydroxyethyl starch is reacted with extracellular hemoglobin, so that the hemoglobin, through primary amine groups of the globin chains reacting with the aldehyde groups of the oxidized starch, covalently binds to the starch through Schiff base linkages. See line 2 on page 8 of the Adamson publication wherein the hydroxyethyl starch starting material used has a molecular weight of from about 70 to about 1000 kDa, which embraces the molecular weight of the hydroxyethyl starch recited in instant Claims 43 and 44. At line 10 of page 8, Adamson discloses that the degree of substitution of the hydroxyethyl groups ranges from about 0.5 to 0.7, which embraces the degree of substitution of the hydroxyalkyl starch molecule recited in instant Claim 45. This description of the Adamson publication embraces the instantly claimed conjugate of hydroxyalkylstarch and a low molecular weight substance.

The Harboe et al publication discloses anti-inflammatory prodrugs of formula PS-O-A-(CH_2)n-B-D, where PS-OH may be selected as hydroxyethyl starch with a molecular wt. (Mw) of 40,000-5,000,000; A is CO or a direct bond; n is 0-14; B = O, CO, NR or a direct bond; R = H or lower alkyl; D = R1CO or R2O; R1COOH and R2OH = antiinflammatory agents (see the Derwent Abstract), which embrace the instantly claimed conjugate of hydroxyalkylstarch and low molecular weight substance. The abstract discloses that the anti-inflammatory prodrugs of the Harboe et al publication are used for treating rheumatism, arthritis, gout, and ulcerative colitis, which embrace the instantly claimed conjugate as a component of a pharmaceutical composition as claimed in instant Claim 56. A list of drugs that can be used in the formula disclosed in the Harboe et al publication are disclosed on pages 6-8 of the Harboe et al publication, which embrace some of the drugs recited in instant Claims 49, 51, 53 and 55.

The Berger et al publication discloses a hydroxyalkyl-starch drug which is used in a composition for controlled release administration of biologically active compounds to animals. Berger et al discloses that bonding of active compounds to the hydroxyalkyl

starch can be a direct reaction. Berger et al discloses that if the active component has a carboxylic acid functional group, it can react directly or indirectly with a hydroxyl group on the hydroxyalkyl starch to form an ester or the active compound can be bound to the hydroxyalkyl starch through a derivative (see page 5, last paragraph). See Scheme I to Scheme III on page 6 of the Berger et al publication for examples of how the active compound may be bonded to the hydroxyalkyl starch polymer which embraces the description of the bonding of the hydroxyalkylstarch to the low molecular weight substance of the instant claims.

One of ordinary skill in this art would be motivated to combine the teaching of the Sommermeyer et al patent with the teachings of the Adamson, Harboe et al and Berger et al publications since each of the references discloses therapeutic applications for hydroxyalkyl starches.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate into the conjugate of the hydroxyalkylstarch and low molecular weight substance of the Sommermeyer et al patent a hydroxyalkylstarch comprising a specific linker, a hydroxyalkylstarch having a specific molecular weight, and a specific type of low molecular weight substance in view of the recongnition in the art, as evidenced by the Adamson, Harboe et al and Berger et al publications, that theses characteristics of the conjugate increases the effectiveness of the conjugate as a therapeutic agent for pharmaceutical applications., which includes making the composition more stable and more effective as a controlled release formulation.

14. Applicant's arguments with respect to Claims 37-56 and 74-78 have been considered but are moot in view of the new ground(s) of rejection.

Summary

15. Claims 37-56 and 74-78 are rejected; Claims 57-73 are withdrawn from consideration as being directed to non-elected inventions.

Examiner's Telephone Number, Fax Number, and Other Information

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Everett White whose telephone number is 571-272-0660. The examiner can normally be reached on 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia A. Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Everett White/
Examiner, Art Unit 1623

/Shaojia Anna Jiang/
Supervisory Patent Examiner, Art Unit 1623